# Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer

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Personal cigarette smoking and exposure to passive smoke as risk factors for cervical cancer were examined in a population-based, case-control study conducted in Utah. Personal cigarette smoking was found to increase the risk of cervical cancer, after adjusting for age, educational level, church attendance, and sexual activity. The adjusted risk estimate associated with being a current smoker was 3.42 (95% confidence interval [CI], 2.10 to 5.57); for having smoked for 5 or more pack-years, it was 2.81 (95% CI, 1.73 to 4.55); and for having smoked at least 100 lifetime cigarettes, it was 2.21 (95% CI, 1.44 to 3.39). The adjusted risk estimate (also adjusted for actual cigarettes smoked) associated with passive smoke exposure for 3 or more hours per day was 2.96 (95% CI, 1.25 to 7.03). Risk from passive smoking was greater in women who were not smokers (odds ratio, 3.43; 95% CI, 1.23 to 9.54) than in women who smoked (odds ratio, 2.59; 95% CI, 0.23 to 29.24).

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IN 1977, Winkelstein[1] hypothesized that cigarette smoking was related to cervical cancer. This hypothesis was based on the observation that cigarette smoking is most strongly associated with squamous cell carcinomas, such as those of the lung and larynx. Squamous cell carcinomas are also the most preponderant histological type among cancers of the cervix uteri. Since 1977, this hypothesis has been expanded[2] and several studies have provided supportive data.[3-6] Passive smoking is the inhalation of smoke from tobacco products used by others. Studies have shown passive smoking to increase the risk of lung cancer,[7-11] although the risk associated with passive smoking and other squamous cell carcinomas has not been studied.

For editorial comment see p 1631.

The purpose of this study was to examine the cervical cancer risk associated with actual cigarette smoking and exposure to passive smoke. Because a large percentage of the population in Utah are members of the Church of Jesus Christ of Latter-day Saints (Mormons), which proscribes the use of tobacco, we were able to examine risk from exposure to passive smoke in nonsmokers as well as in smokers.

## METHODS

A population-based, case-control study was conducted in the urban areas of Utah between 1984 and 1987. Women who were residing in Salt Lake, Davis, Weber, and Utah counties (the Wasatch Front) and who were between the ages of 20 and 59 years were eligible for inclusion in the study. This study was restricted to white women because less than 5% of the Utah population is nonwhite.

### Study Population

A rapid reporting system was used to identify cases of cervical cancer within 6 weeks of diagnosis. Using this system, all 15 pathology laboratories along the Wasatch Front were visited monthly, and histological slides for cases of severe dysplasia, carcinoma in situ (CIS), and invasive squamous cell carcinoma of the cervix uteri were retrieved. A single study pathologist reviewed all slides in a blind manner and made the final determination of disease classification and eligibility for inclusion in the study. Based on the diagnosis of the study pathologist, women who had a first, primary cancer diagnosis of in situ or invasive squamous cell carcinoma of the cervix (International Classification of Diseases oncology code 180) were included in the study. The Utah Cancer Registry was used to verify complete case ascertainment. Histological material for women identified through the Utah Cancer Registry was also reviewed by the study pathologist. From a total of 350 women with CIS and 60 women with invasive carcinoma, 234 women (67%) with CIS and 36 women (60%) with invasive carcinoma were interviewed (66%). Four cases were excluded because of missing or unreliable data.

Controls were selected to categorically match cases in 5-year age intervals and by the county of residence using a random-digit–dialing telephone sam-

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pling technique.[12] Of the 635 controls identified, 480 (76%) agreed to be interviewed. Women who had a hysterectomy prior to 1984 were excluded, and 6 additional controls were excluded because of missing or unreliable data. A more detailed description of study completion rates is presented elsewhere.[13]

### Data Collection

Personal interviews were conducted in the respondents' homes by trained interviewers and lasted approximately 1½ to 2 hours. Information obtained included (1) demographic data such as age, marital status, religious preference, church attendance practices, education, and income; (2) detailed dietary intake data; (3) lifetime cigarette usage; (4) the level of exposure to passive smoke; (5) a limited medical history; (6) use of contraceptives; and (7) a self-administered sexual history questionnaire. Additionally, women were asked to voluntarily give 20 mL of blood so that the presence or absence of antibodies to herpes simplex virus could be ascertained. Serum cotinine levels were determined by the method described by Haley et al[14] to validate self-reported smoking practices. Five hundred forty-two women (80% of cases and 81% of controls) agreed to have their blood drawn.

Cigarette-use questions included whether they had ever smoked 100 or more cigarettes in their lifetime, the age of smoking initiation, if they smoked continuously from the time they started, their inhalation practices, the number of years they had smoked, and the average number of cigarettes smoked per day. The last two variables were used to calculate the pack-year smoking history for each woman. It was also ascertained if the women had smoked cigarettes during the past 3 days, so that recent cigarette smoking practices could be compared with the results of the serum cotinine assays.

Several questions were asked about exposure to passive smoke. These questions had been pilot tested in a previous case-control study of similarly aged women and modified based on their responses. Women were asked if during the past 5 years they were exposed to "a lot, some, a little, or none at all" of smoking by others both inside and away from their homes. These categories were based on the methodology developed by Jarvis et al[15] to quantify passive smoking exposure. Additionally, women were asked to give an estimate of the number of hours per day, week, or month they were exposed to cigarette smoke both inside and away from their homes for the past 5 years. The period of 5 years prior to interview was chosen to be consistent with methods used by others[16] and to provide a reference period prior to disease.

Table 1.—Characteristics of Study Population

| Characteristics | No. (%) of Women: Cases (n = 256) | Controls (n = 408) |
|---|---|---|
| Carcinoma in situ | 231 (87) | |
| Invasive carcinoma | 35 (13) | |
| Age, y | | |
| 20-29 | 92 (35) | 143 (35) |
| 30-39 | 123 (46) | 159 (39) |
| 40-49 | 37 (14) | 71 (17) |
| 50-59 | 14 (5) | 35 (9) |
| Education | | |
| <High school | 135 (51) | 100 (25) |
| High school | 115 (43) | 252 (62) |
| >High school | 16 (6) | 56 (14) |
| Religion | | |
| LDS* | 113 (42) | 267 (65) |
| Non-LDS | 153 (58) | 141 (35) |
| Church attendance | | |
| <1/mo | 191 (72) | 132 (32) |
| 1-3/mo | 26 (10) | 38 (9) |
| ≥1/wk | 49 (18) | 238 (58) |
| No. of sexual partners of woman† | | |
| ≤1 | 25 (10) | 210 (52) |
| 2-3 | 54 (21) | 73 (18) |
| 4-5 | 47 (19) | 53 (13) |
| 6-10 | 57 (23) | 39 (10) |
| >10 | 69 (27) | 28 (7) |

*LDS indicates members of the Church of Jesus Christ of Latter-day Saints.
†Some women did not complete the confidential questionnaire that contained sexual history.

### Data Analyses

Results from the crude analyses were similar for CIS and invasive cervical cancer cases, and, thus, the results presented herein include all CIS and invasive cases combined and compared with controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the risk of cervical cancer associated with cigarette smoking and exposure to passive smoke. Stratified analyses were used to identify potential confounding variables. Socioeconomic status, as reflected by education and income; sexual activity; and frequency of church attendance were found to be confounding variables in this study and have been reported as risk factors for cervical cancer by others.[16-18] These variables were further tested in multiple logistic analyses to determine which variables resulted in the best-fitting logistic model. Multiple logistic regression models were used to remove the confounding effects of these associated variables on the smoking and cervical cancer relation and to determine if significant linear associations existed.[19]

It is difficult to offer a biologic explanation for the relationship of church attendance and educational level (as an indicator of socioeconomic status) to cervical cancer risk; however, both of these variables were controlled for in the final multiple logistic regression models because we believe they are proxies for some unidentified confounding variables. Age was also controlled in the final models, because slight confounding was present from this variable. Sexual activity was found to be the major confounding variable in this study, as it had the greatest effect on the risk estimates for smoking as well as contributed the most to the fit of the logistic models. The risk associated with passive smoking was assessed separately in smokers and nonsmokers. Interaction between passive smoking and actual cigarette smoking was also assessed by both multiplicative and additive models as described by Rothman.[20]

## RESULTS

The characteristics of the study population are given in Table 1. Eighty-seven percent of the cases had CIS and 13% had invasive carcinomas. Cases tended to have lower levels of education and income (income not shown) and a greater number of sexual partners than did controls. Controls more frequently reported being members of the Church of Jesus Christ of Latter-day Saints and attending church at least once per week. Church attendance was a proxy measure for adherence to the church teachings.

To validate cigarette smoking prac-

Table 2.—Comparison of Reported Cigarette Smoking During the 3 Days Prior to Interview and Measurement of Serum Cotinine Levels

| Smoking Status | Cotinine Level | | |
|---|---|---|---|
| | None Detected | 1-15 ng/mL | >15 ng/mL |
| Cases (n = 212) | | | |
| Reported nonsmoker | 90 | 3 | 4 |
| Reported smoker | 1 | 2 | 112 |
| Controls (n = 330) | | | |
| Reported nonsmoker | 285 | 3 | 4 |
| Reported smoker | 1 | 0 | 37 |

Table 3.—Cervical Cancer Risk Associated With Cigarette Smoking

| Cigarette Smoking | No. of Cases | No. of Controls | Odds Ratio (95% Confidence Interval)* | |
|---|---|---|---|---|
| | | | Crude | Adjusted |
| Smoking status | | | | |
| Never | 81 | 305 | 1.00† | 1.00† |
| Ex-smoker | 37 | 48 | 2.90 (1.79-4.70) | 1.41 (0.82-2.45) |
| Current smoker | 148 | 55 | 10.13 (7.00-14.67) | 3.42 (2.10-5.57) |
| Cigarette smoker | | | | |
| <100 Cigarettes | 81 | 305 | 1.00† | 1.00† |
| ≥100 Cigarettes | 185 | 103 | 6.76 (4.86-9.41) | 2.21 (1.44-3.39) |
| No. of cigarettes/d | | | | |
| None | 81 | 305 | 1.00† | 1.00† |
| 1-15 | 84 | 51 | 6.20 (4.14-9.29) | 2.23 (1.34-3.69) |
| >15 | 101 | 52 | 7.31 (4.94-10.82) | 2.19 (1.33-3.62) |
| No. of years smoked | | | | |
| None | 81 | 305 | 1.00† | 1.00† |
| 0.001-10 | 75 | 42 | 6.72 (4.40-10.27) | 1.68 (1.01-2.80) |
| >10 | 110 | 81 | 6.79 (4.85-9.91) | 2.17 (1.20-3.90) |
| Pack-years | | | | |
| None | 81 | 305 | 1.00† | 1.00† |
| 0.05-5 | 47 | 29 | 6.10 (3.75-9.94) | 1.50 (0.87-2.59) |
| >5 | 138 | 74 | 7.02 (4.91-10.03) | 2.81 (1.73-4.55) |
| Continuous smoker | | | | |
| Never smoked | 81 | 305 | 1.00† | 1.00† |
| Start and stop | 81 | 58 | 5.25 (3.53-7.84) | 1.61 (0.97-2.67) |
| Continuous | 104 | 45 | 8.70 (5.84-12.92) | 3.00 (1.80-4.99) |
| Inhale | | | | |
| Nonsmoker | 81 | 305 | 1.00† | 1.00† |
| Mouth/throat | 25 | 9 | 10.46 (5.29-20.67) | 3.32 (1.38-7.97) |
| Chest | 159 | 92 | 6.50 (4.63-9.15) | 2.34 (1.52-3.61) |
| Age first smoked, y | | | | |
| Never | 81 | 305 | 1.00† | 1.00† |
| >16 | 86 | 56 | 5.88 (3.95-8.77) | 2.43 (1.38-3.70) |
| ≤16 | 99 | 48 | 7.76 (5.22-11.58) | 2.58 (1.54-4.31) |

*Odds ratios and 95% confidence intervals were calculated from multiple logistic regression analyses and adjusted for age, church attendance, education, and number of sexual partners of the woman.
†All values compared with the lowest level.

tices, we compared reported cigarette smoking during the 3 days prior to the interview with serum cotinine levels. Women were divided into 3 groups, those who had no detectable levels of serum cotinine, those who had low levels of serum cotinine, and those who had serum cotinine levels above 15 ng/mL (Table 2). In most instances, low levels of cotinine may not represent actual cigarette smoking, but may indicate exposure to passive smoke. While we did not observe serum cotinine levels to be sensitive to reported exposure to passive smoke, others have reported serum cotinine levels for exposure to passive smoke between 0.5% and 6.0% of the mean reported for cigarette smokers.[11] Therefore, we have used a cut-off point for serum cotinine of 15 ng/mL to assess the validity of reported smoking practices.

Of women who reported not smoking, only 4 cases and 4 controls had levels of serum cotinine above 15 ng/mL, and only 2 cases and 1 control had levels above 50 ng/mL. We have also compared women who reported smoking 3 days prior to the interview and those who also reported having smoked 100 or more cigarettes during their lifetime. We found that none of the women who reported smoking fewer than 100 cigarettes in their lifetime reported smoking during the 3 days prior to interview; however, 99 women said they did not smoke during the past 3 days, although they had smoked at least 100 cigarettes during their lifetime. Because of the excellent agreement between reported cigarette smoking practices and serum cotinine levels and because all of the respondents reported cigarette use history, the reported cigarette history is used in these analyses.

### Personal Smoking Risk

Assessment of cervical cancer risk associated with cigarette smoking practices is shown in Table 3. More than half of the cases (148 [56%]) reported cigarette smoking while most of the controls (305 [75%]) reported never smoking cigarettes. Risk estimates associated with smoking were greatly attenuated by sexual history, reflected by the number of sexual partners of the woman. All cigarette smoking practices gave similar estimates of risk, with an adjusted risk for current smokers of 3.42 (95% CI, 2.10 to 5.57); for smoking 100 or more cigarettes during the lifetime it was 2.21 (95% CI, 1.44 to 3.39); for smoking more than 15 cigarettes per day it was 2.19 (95% CI, 1.33 to 3.62; $P = .001$, for linear trend). The risk associated with smoking for 5 pack-years was 2.81 (95% CI, 1.73 to 4.55; $P = .0035$, for linear trend), and for smoking for more than 10 years it was 2.17 (95% CI, 1.20 to 3.90; $P = .0029$, for linear trend). Women who first started to smoke when they were 16 years of age or younger had an adjusted risk estimate of 2.58 (95% CI, 1.54 to 4.31). Likewise, women were at a greater risk if they smoked continuously (adjusted OR, 3.00; 95% CI, 1.80 to 4.99) than if they started and stopped (adjusted OR, 1.61; 95% CI, 0.97 to 2.67).

We further explored the effects of having smoked 100 or more cigarettes ("ever smoked") vs never having smoked 100 cigarettes for different age and sexual activity groups (Table 4). Cigarette smoking was a greater risk factor for cervical cancer in women under 30 years of age than in women older than 30 years, with an OR of 6.81 (95% CI, 3.28 to 14.14) being observed for ever having smoked. Women who smoked but had one or fewer sexual partners experienced the greatest risk from cigarette smoking, with an OR of 14.19 (95% CI, 9.17 to 38.92) being observed. This finding could reflect the fact that cigarette smoking is a more important risk factor in women who have not experienced other major risk factors.

### Passive Smoking Risk

Exposure to passive smoke was an independent risk factor for cervical can-

cer (Table 5). The risk estimate associated with an exposure to passive smoke for 3 or more hours a day was 2.96 (95% CI, 1.25 to 7.03; $P = .0028$, for linear trend), after adjusting for age, years of education, church attendance, number of sexual partners, and pack-years of cigarettes smoked (Table 5). (Analyses were also done that controlled for the number of sexual partners of the mate; however, because approximately 100 women did not report the sexual history of their current mate and because results were similar to those observed when controlling for the number of sexual partners of the women, the results presented are adjusted for number of sexual partners of the woman.)

Exposure to passive smoke in the home was a greater risk factor than exposure to passive smoke away from the home. The OR associated with exposure to greater than 1.5 hours per day of passive smoke in the home was 2.29 (95% CI, 1.39 to 3.77; $P = .0041$, for linear trend); while the risk associated with smoke away from home was 1.48 (95% CI, 0.74 to 2.95; $P = .0781$, for linear trend). Similar estimates of risk were seen when women reported the actual number of hours of exposure to passive smoke as when they reported exposure as "none, a little, some, or a lot." Again, exposure to a lot of passive smoke in the home resulted in a twofold increased risk of developing cervical cancer. Analyses of risk associated with passive smoking by age and sexual activity groups showed that women who were 40 years or older were at a greater risk from exposure to passive smoking after controlling for number of sexual partners and actual smoking (OR, 11.71; 95% CI, 2.24 to 61.24) than were women younger than 40 years. No differences in risk by the number of sexual partners of the woman were observed, with the highest level of passive smoke exposure resulting in a twofold to threefold increased risk in all groups.

Because risk associated with exposure to passive smoke may be different in smokers and nonsmokers, we stratified for smoking status and assessed the risk of passive smoking in these two groups (Table 6). Exposure to 3 or more hours of passive smoke in nonsmokers resulted in an increased risk of 3.43 (95% CI, 1.23 to 9.54; $P = .0179$, for linear trend). The risk was less when we looked at the lower levels of exposure (0.01 to 1.5 h/d) either in the home or away from the home (OR, 2.66 and 2.30, respectively; $P = .0362$ and $P = .0994$, for linear trend, respectively). Because few smokers were not exposed to passive smoke, it was more difficult to assess the risk of passive smoking in smokers. Although, there was insufficient power in our study to detect a statistically significant difference between levels of exposure, increasing levels of exposure resulted in an increasing risk for cervical cancer, with smokers exposed to 3 or more hours of passive smoke per day having an increased risk of 2.59 (95% CI, 0.23 to 29.24; $P = .1298$, for linear trend). Further analyses of interaction, by the methods described by Rothman[28] between passive smoking and actual cigarette smoking, showed interaction between these two variables.

Table 4.—Cervical Cancer Risk Associated With Cigarette Smoking by Age and Number of Sexual Partners

| Characteristics | No. of Cases | | No. of Controls | | Adjusted Odds Ratio* (95% Confidence Interval) |
|---|---|---|---|---|---|
| | Non-smokers | Smokers | Non-smokers | Smokers | |
| Age, y | | | | | |
| 20-29 | 18 | 74 | 110 | 33 | 6.81 (3.26-14.14) |
| 30-39 | 43 | 80 | 117 | 42 | 3.04 (1.72-5.37) |
| 40-59 | 20 | 31 | 78 | 28 | 2.30 (1.02-5.33) |
| No. of sexual partners of woman | | | | | |
| 0-1 | 13 | 12 | 197 | 13 | 14.19 (5.17-38.92) |
| 2-3 | 19 | 35 | 51 | 22 | 4.51 (2.08-9.79) |
| ≥4 | 46 | 127 | 54 | 66 | 2.34 (1.42-3.87) |

*Compares smokers relative to nonsmokers within various strata of age and number of sexual partners. Odds ratios for age were also adjusted for number of sexual partners; odds ratios for number of sexual partners were also adjusted for age.

Table 5.—Cervical Cancer Risk Associated With Exposure to Passive Smoke

| Exposure | No. of Cases | No. of Controls | Odds Ratio (95% Confidence Interval) | |
|---|---|---|---|---|
| | | | Crude | Adjusted* |
| Passive smoke, h/d | | | | |
| None | 9 | 78 | 1.00† | 1.00† |
| 0.1-0.9 | 53 | 169 | 2.71 (1.30-5.67) | 1.20 (0.52-2.76) |
| 1.0-2.9 | 43 | 64 | 5.68 (2.70-11.97) | 1.60 (0.65-3.96) |
| ≥3.0 | 161 | 94 | 14.84 (7.96-27.67) | 2.96 (1.25-7.03) |
| In-home passive smoke, h/d | | | | |
| None | 80 | 278 | 1.00† | 1.00† |
| 0.1-1.5 | 52 | 63 | 2.86 (1.86-4.43) | 0.97 (0.56-1.68) |
| >1.5 | 134 | 66 | 7.05 (4.86-10.20) | 2.29 (1.39-3.77) |
| Away-from-home passive smoke, h/d | | | | |
| None | 22 | 88 | 1.00† | 1.00† |
| 0.1-1.5 | 130 | 234 | 2.22 (1.34-3.69) | 1.07 (0.57-2.00) |
| >1.5 | 114 | 84 | 5.42 (3.22-9.15) | 1.48 (0.74-2.95) |
| In-home passive smoke | | | | |
| None | 80 | 277 | 1.00† | 1.00† |
| Little | 32 | 44 | 2.51 (1.51-4.19) | 0.94 (0.51-1.73) |
| Some | 57 | 40 | 4.93 (3.14-7.76) | 1.81 (1.02-3.24) |
| A lot | 97 | 45 | 7.46 (4.96-11.22) | 2.04 (1.18-3.51) |
| Away-from-home passive smoke | | | | |
| None | 22 | 87 | 1.00† | 1.00† |
| Little | 54 | 104 | 2.05 (1.18-3.62) | 1.06 (0.54-2.17) |
| Some | 99 | 150 | 2.61 (1.55-4.40) | 1.02 (0.53-1.99) |
| A lot | 91 | 86 | 5.45 (3.17-9.39) | 1.38 (0.68-2.81) |

*Odds ratios and 95% confidence intervals are adjusted for age, education, church attendance, number of sexual partners of the woman, and cigarette smoking.
†All values compared with the lowest level.

## COMMENT

The results from this study support previous research that has shown that women who smoke cigarettes are at an increased risk of developing cervical cancer. The risk is greatest in women less than 30 years of age and in women who have had one or fewer sexual partners. This is probably because cigarette smoking will be a greater risk factor in women who do not have other major competing risk factors. The risk estimates for cigarette smoking observed by other investigators[2-4] are comparable with the adjusted OR of 2.2 observed in this study. Other studies[4-6] have shown risk estimates slightly lower than those we observed, which ranged from 1.5 to 1.8. A case-control study of 332 white women with cervical cancer and 1725 white controls by Stellman and colleagues[29] did not show cigarette smoking to be related to cervical cancer after adjusting for age and socioeconomic sta-

Table 6.—Cervical Cancer Risk Associated With Exposure to Passive Smoke in Cigarette Nonsmokers and Smokers*

| Exposure | Odds Ratio (95% Confidence Interval) | |
|---|---|---|
| | Nonsmokers† | Smokers‡ |
| All passive smoke, h/d | | |
| None | 1.00§ | 1.00§ |
| 0.1-0.9 | 1.14 (0.45-2.94) | 1.64 (0.14-19.31) |
| 1.0-2.9 | 1.57 (0.52-4.73) | 1.75 (0.15-20.03) |
| ≥3.0 | 3.43 (1.23-9.54) | 2.59 (0.23-29.24) |
| In-home passive smoke, h/d | | |
| None | 1.00§ | 1.00§ |
| 0.1-1.5 | 0.62 (0.25-1.53) | 1.18 (0.54-2.53) |
| >1.5 | 2.66 (1.15-6.13) | 1.89 (0.94-3.79) |
| Away-from-home passive smoke, h/d | | |
| None | 1.00§ | 1.00§ |
| 0.1-1.5 | 1.33 (0.58-3.07) | 0.80 (0.25-2.63) |
| >1.5 | 2.30 (0.89-5.95) | 0.73 (0.22-2.44) |
| In-home passive smoke | | |
| None | 1.00§ | 1.00§ |
| Little | 1.86 (0.37-9.37) | 1.60 (0.59-4.34) |
| Some | 1.49 (0.44-5.09) | 2.47 (1.07-5.70) |
| A lot | 2.93 (1.08-7.94) | 1.26 (0.64-2.50) |
| Away-from-home passive smoke | | |
| None | 1.00§ | 1.00§ |
| Little | 1.58 (0.68-3.68) | 0.87 (0.40-1.91) |
| Some | 1.11 (0.49-2.50) | 0.76 (0.38-1.52) |
| A lot | 1.59 (0.57-4.45) | 0.67 (0.32-1.40) |

*Nonsmokers are defined as women who have smoked fewer than 100 cigarettes in their lives; smokers have smoked 100 or more cigarettes.

†Odds ratios and 95% confidence intervals were calculated from multiple logistic regression analyses and adjusted for age, education, church attendance, and number of sexual partners of the woman.

‡Also was adjusted for the number of cigarette pack-years.

§All values compared with the lowest level.

tus. A possible explanation for these conflicting results could be that the study by Stellman et al was not population based. Their cases were originally used as controls in another study, and their control group consisted of women hospitalized for nonneoplastic diseases. A study by West and colleagues[28] compared smoking and cervical cancer risks obtained from a population-based study with a hospital-based study and found that the risk for smoking and cervical cancer, as well as for several other risk factors, were lower in the hospital-based study because of the more "case-like" attributes of the control group.

We have shown that women who are exposed to the cigarette smoke of others are at an increased risk of cervical cancer. This increased risk is independent of the risks associated with personal cigarette smoking, educational level, church attendance, age, and number of sexual partners, although the greatest risk was in women who were nonsmokers. The risk associated with passive smoking in this study is as strong as that observed from personal cigarette smoking. While all smokers are exposed to their own smoke, few smokers reported not also being exposed to smoke by others. It is possible that there is more misclassification of passive smoking in smokers than in nonsmokers.

Few studies have looked at passive smoking and cervical cancer risk. Two studies[24,25] have looked at the husbands' smoking habits as a risk factor for cervical cancer. Hellberg et al[24] found that although smoking by the male partner was correlated with cervical cancer, this relationship disappeared when adjusting for the smoking habits of the woman. This study did not have sufficient sample size to assess the effect that the male partners who smoked had on nonsmoking cases. The study by Buckley et al[25] found a twofold increase in cervical cancer risk if the husband smoked. While they adjusted for sexual partners of the men, they did not adjust for smoking practices of the women.

The mechanisms whereby cigarette smoking may increase the risk of cervical cancer are beginning to be evaluated. Recent studies have shown that constituents from cigarette smoke can be transmitted through the blood to distant tissues and organs, and these substances have been detected in the uterine cervix of cigarette smokers.[29-31] Tobacco smoke is known to contain mutagens and carcinogens that may act as initiators and/or promoters in the uterine cervix, although no specific mutagens have been identified in cervical fluid.

Carcinogens in mainstream smoke (smoke inhaled from smoking) and sidestream smoke (smoke inhaled from being in areas where other people smoke) have been evaluated.[21,32,33] It has been shown that some substances, such as nitrosamines, occur in higher concentrations in side-stream smoke than in mainstream smoke.[5,34,35] Of interest in another analysis of our study population, the intake of vitamins C and E was found to be related to lower cervical cancer risk in smokers.[13] Both of these vitamins are known to be antagonists to nitrosamines.[36,37] Comparative estimates have been made regarding inhalation of passive smoke vs inhalation of substances while smoking. In 1 hour of passive smoking, it is estimated that particulate matter such as nicotine would be inhaled in one fourth to one fiftieth of that inhaled by smoking one cigarette,[38] while during the same amount of time, the exposure to nitrosamines is equivalent to smoking one-half pack of filtered cigarettes.[39]

We have also shown that personal cigarette smoking has an additive effect with passive smoke exposure. The combined risk of being a cigarette smoker and also being exposed to the tobacco smoke of others is greater than that observed for either risk factor separately. This finding needs to be verified in other studies designed to ascertain both passive and actual smoking and the cervical cancer risk.

In epidemiologic studies, determination of smoking status generally has relied on self-reported information. The validity of self-report data has been challenged, particularly in settings where the respondent perceived pressure to quit smoking, such as in smoking cessation programs.[40] An analogous situation is the proscription of the Church of Jesus Christ of Latter-day Saints against the use of tobacco products, which might lead some women to report their smoking practices inaccurately.

A strength of this investigation was the validation of reported smoking status with serum cotinine levels. The concentration of cotinine, regardless of whether from serum, saliva, or urine, has been demonstrated to be better than other smoking status tests.[41] Urinary cotinine levels are preferred as an indicator of passive smoking exposure.[42] The present findings support the inadequacy of serum cotinine for determination and quantification of passive smoke exposure since less than 2% of the study population fell within the 1- to 15-ng/mL range, whereas 47% reported some passive exposure in the home. We feel that this level of agreement is excellent, especially because the Church of Jesus Christ of Latter-day Saints proscribes the use of tobacco.

A second major strength of our inves-

tigation was the population studied. Because a large segment of this population did not smoke cigarettes, we were able to assess passive smoking risk in nonsmokers as well as smokers. We evaluated several indicators of exposure to passive smoke and found that, regardless of the indicator used, the results were consistent. A third study strength is that a single study pathologist reviewed all the histological material of potential cases and made the final determination of eligibility so that we had consistent case definition. In addition to these other strengths, we have used community-based controls. We have also been able to assess the risk of cigarette smoking independently of sexual behavior. However, because of the strong association between sexual activity and cervical cancer risk and the strong association of sexual activity and smoking status, misclassification of sexual history could result in inflated risk estimates for smoking from uncontrolled confounding.

A limitation of our study was that only 66% of the cases and 76% of the potential controls completed the interview process. Completion rates of this magnitude are common in studies of cervical cancer where the population is often young, of low socioeconomic status, and highly mobile. Some studies have reported response rates of less than 50%.[40] We do not know the effects of nonresponse on our study results. Additionally, because only 35 cases of invasive cervical cancer had complete data for analysis, it was difficult to assess risk separately for invasive cancers. We did attempt to determine if cigarette smoking presented a greater risk for CIS than for invasive carcinomas. We did not see any differences and, therefore, combined the two groups for the final analyses. Others[41-43] have examined cigarette smoking in patients with CIS and invasive cervical cancer and likewise did not see differences in effect for these two categories of cervical cancer.

In summary, it seems that exposure to passive cigarette smoke and personal cigarette smoking are important in the etiology of cervical cancer. Exposure to passive cigarette smoke increases cervical cancer risk, especially in nonsmokers. The greatest risk associated with passive smoking is that inhaled in the home, possibly because people exposed to smoke at home incur larger doses of exposure either from being in a more confined area or having a more constant exposure. Further assessment of the effects of passive smoke on squamous cell carcinomas seems warranted. Additionally, studies that identify specific mutagens in cervical fluids of women exposed to large amounts of passive smoke would provide support for this observation.

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